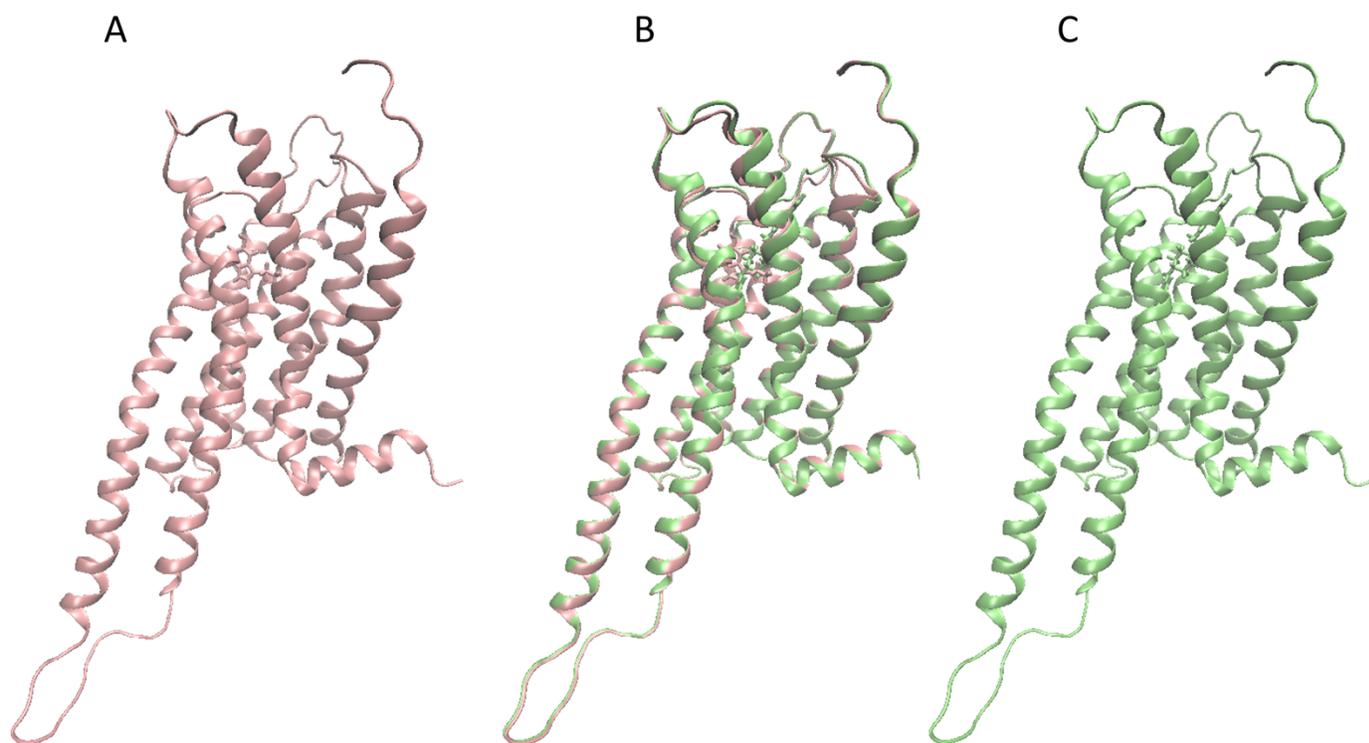


Figure S1: contact map

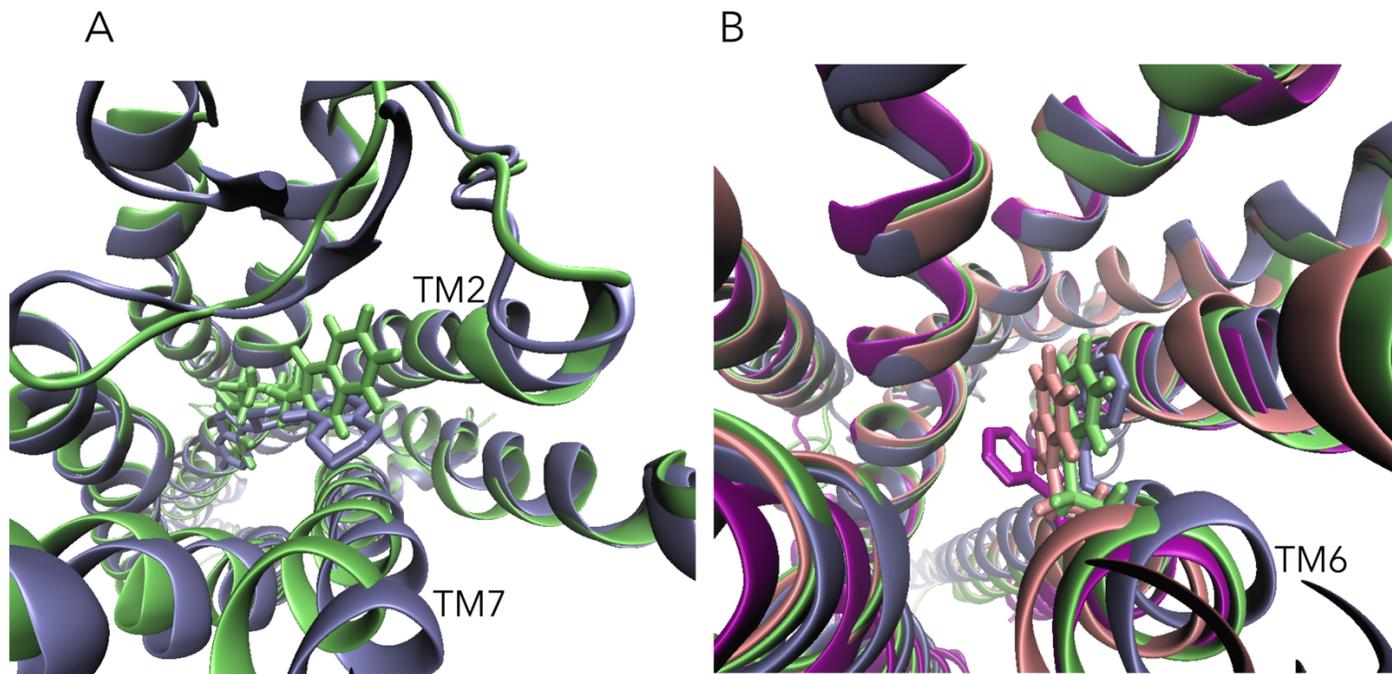


**Figure S2: starting structures**

Panel A – 5-HT<sub>2A</sub>R/5-HT complex starting structure

Panel C – 5-HT<sub>2A</sub>R/KET complex starting structure

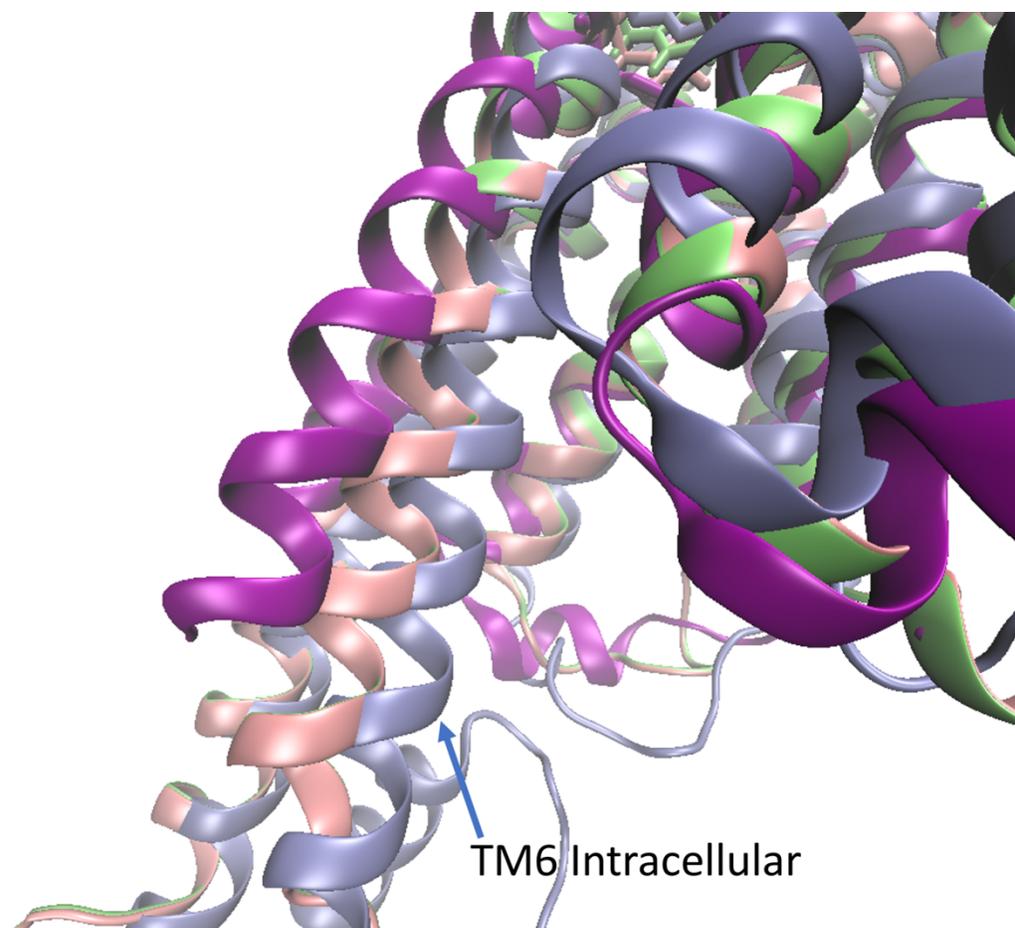
Panel B – 5-HT<sub>2A</sub>R/5-HT and 5-HT<sub>2A</sub>R/KET starting structures overlaid



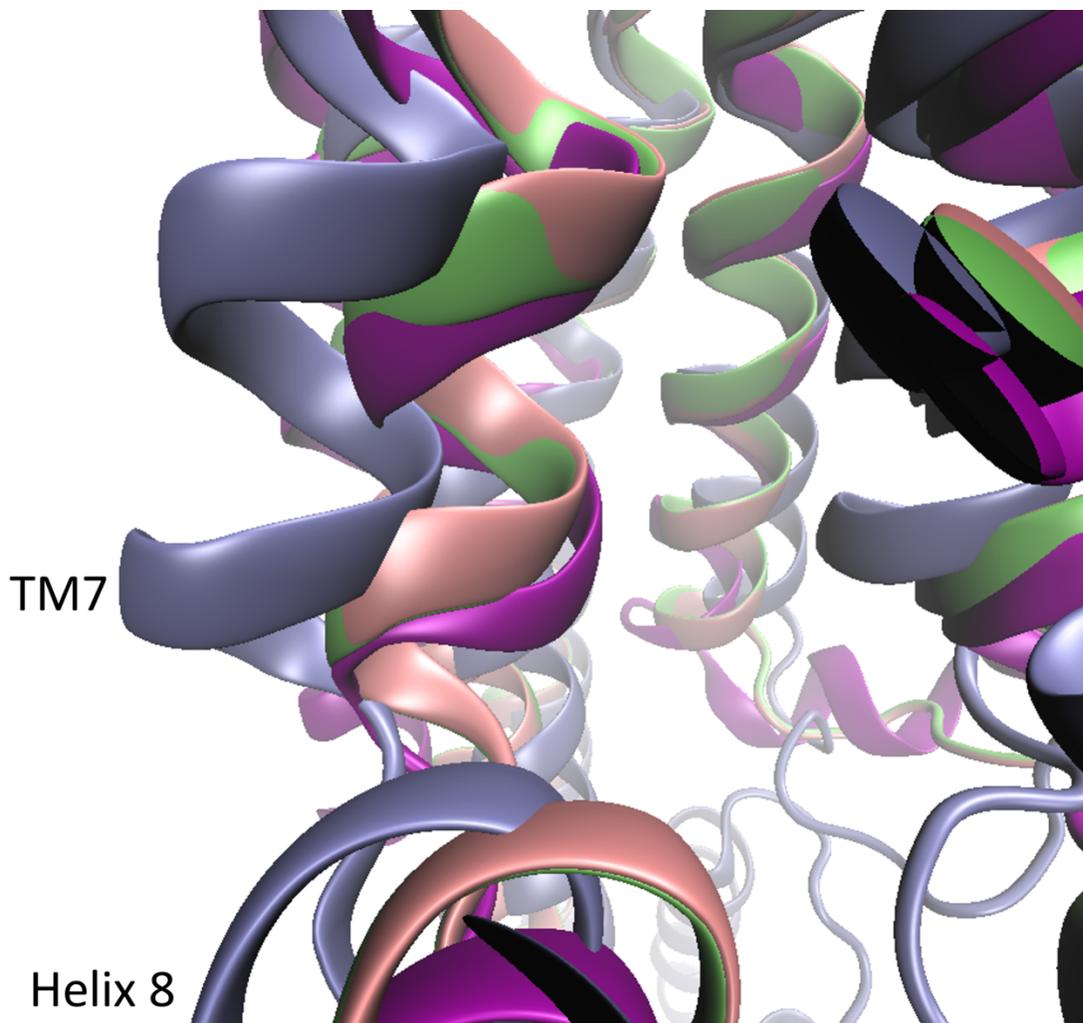
**Figure S3: binding pocket**

Panel A - 5-HT<sub>2A</sub>R/risperidone complex (blue, pdb 6A93) superposed with 5-HT<sub>2A</sub>R/KET starting structure (green)

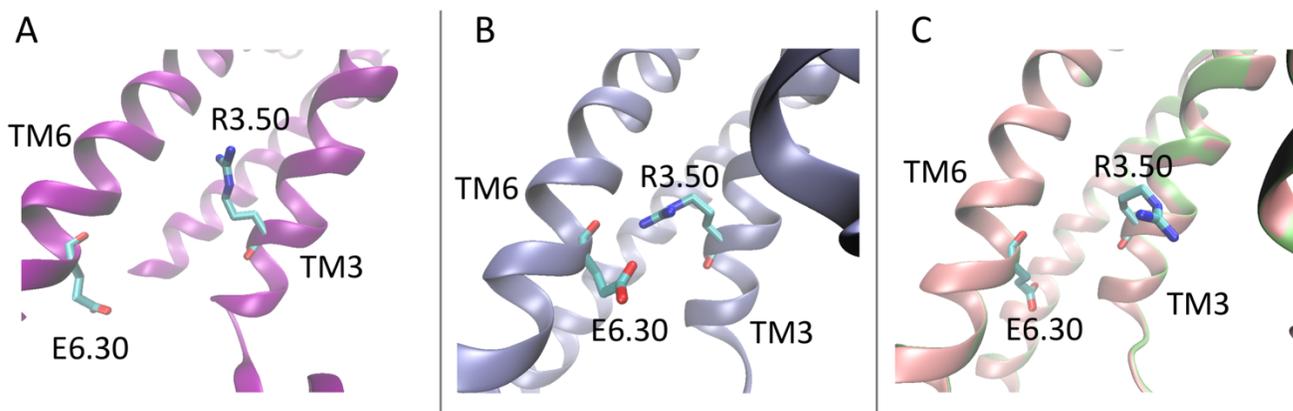
Panel B - “toggle switch” W6.48 (shown in stick model) for the 5-HT<sub>2A</sub>R/risperidone (blue), 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet), 5-HT<sub>2A</sub>R/KET (green), and 5-HT<sub>2A</sub>R/5-HT (coral) structures



**Figure S4:** TM6 movements in as observed in inactive and active states of the 5-HT<sub>2A</sub>R  
5-HT<sub>2A</sub>R/risperidone (blue), 5-HT<sub>2A</sub>R/KET (green), 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet), and 5-HT<sub>2A</sub>R/5-HT (coral)



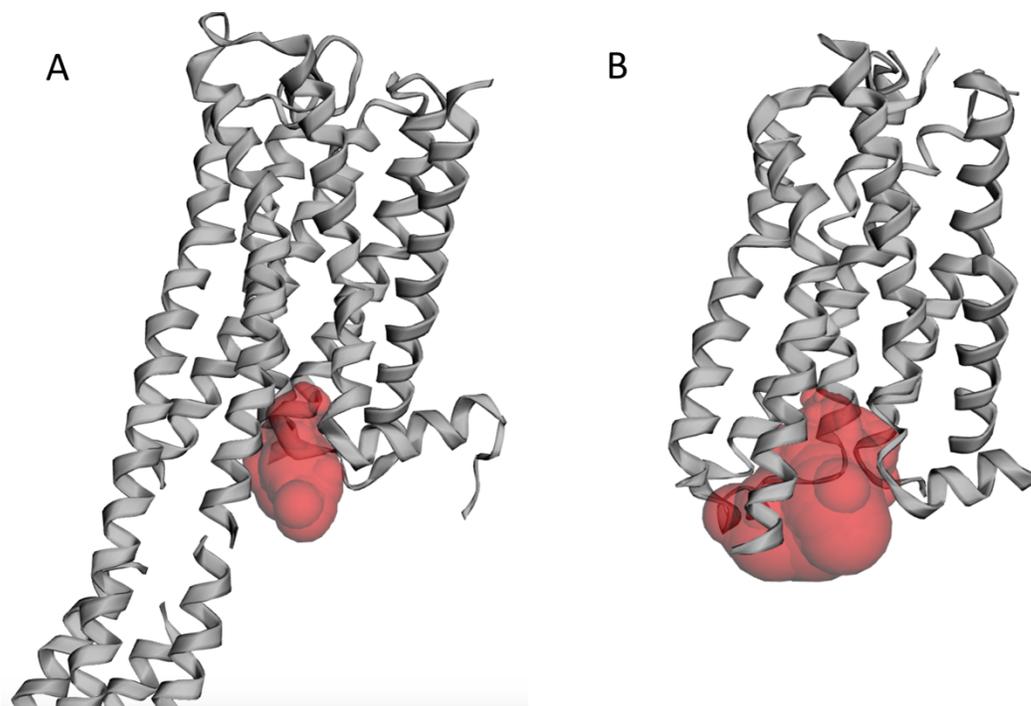
**Figure S5:** TM7 movements in as observed in inactive and active states of the 5-HT<sub>2A</sub>R 5-HT<sub>2A</sub>R/risperidone (blue), 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet), 5-HT<sub>2A</sub>R/KET (green), and 5-HT<sub>2A</sub>R/5-HT (coral)



**Figure S6:** Movements of the ionic lock in inactive and active states of the 5-HT<sub>2A</sub>R

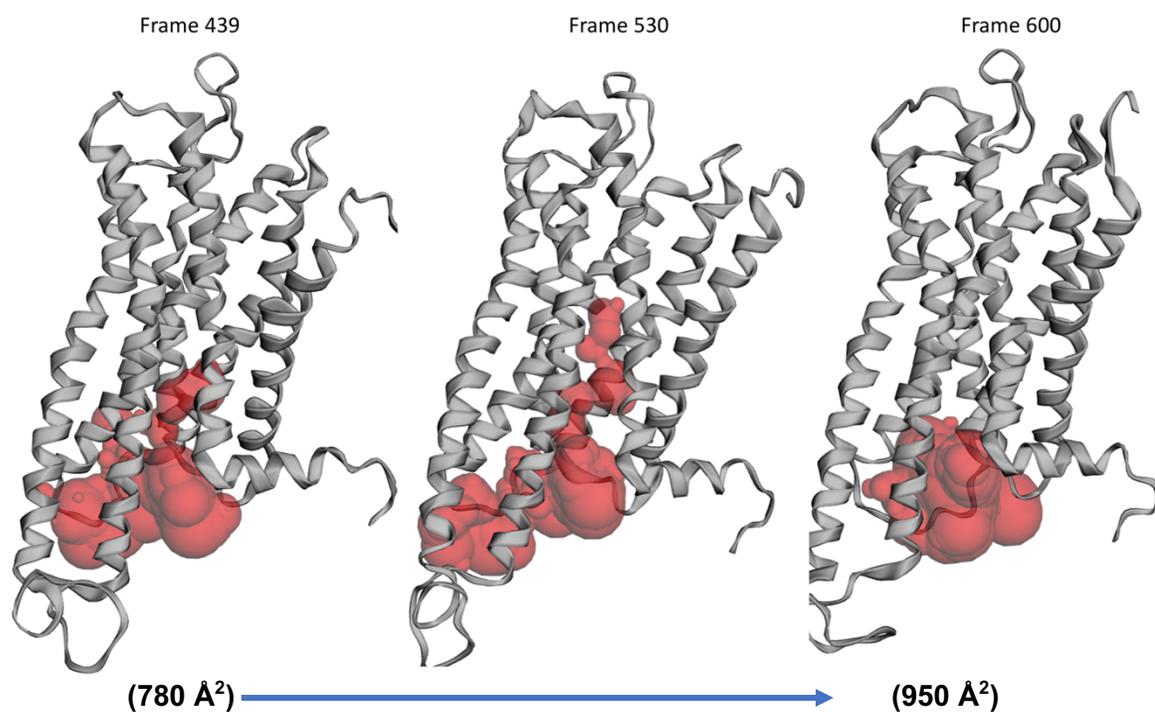
5-HT<sub>2A</sub>R/risperidone (blue), 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet), 5-HT<sub>2A</sub>R/KET (green), and 5-HT<sub>2A</sub>R/5-HT (coral)

Panel A - 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet, pdb 6WHA) with ionic lock (R3.50-E6.30) shown in stick model. Panel B - 5-HT<sub>2A</sub>R/risperidone (blue), with ionic lock (R3.50-E6.30) shown in stick model. Panel C - 5-HT<sub>2A</sub>R/KET (green) and 5-HT<sub>2A</sub>R/5-HT (coral) superposed, with ionic lock (R3.50-E6.30) shown in stick model.



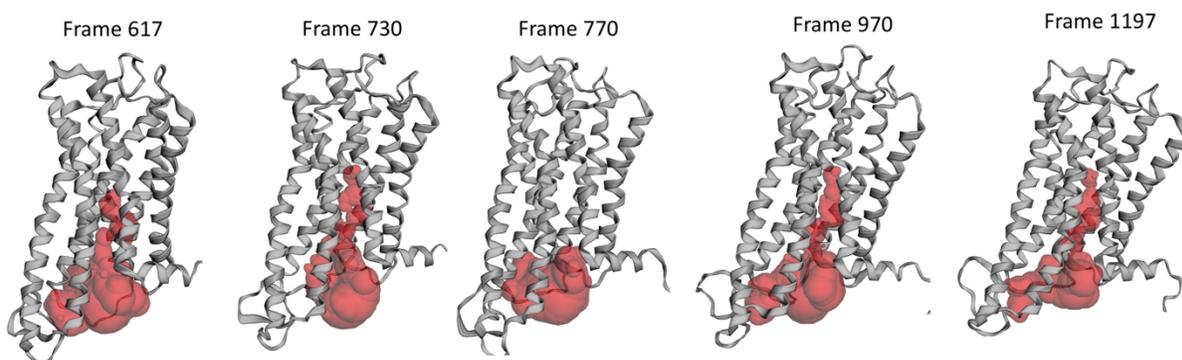
**Figure S7:** Intracellular cavity volumes (inactive and activated states)

Volume of the intracellular cavity of active and inactive state 5-HT<sub>2A</sub>R structures. Panel A: 5-HT<sub>2A</sub>R/risperidone (pdb 6A93) structure is shown in grey, with the intracellular cavity volume computed by the CASTp server shown in red. Panel B: 5-HT<sub>2A</sub>R/25-CN-NBOH/G<sub>q</sub> (violet) (pdb 6WHA) structure is shown in grey, with the intracellular cavity volume computed by the CASTp server shown in red.



**Figure S8:** Intracellular cavity volumes changes during activation

Volume of the intracellular cavity, calculated by CASTp webserver, of the 5HT-bound 5-HT<sub>2A</sub>R trajectory at frames corresponding to **Fig1E-G**.



**Figure S9:** Intracellular cavity volumes changes during inactivation

Volume of the intracellular cavity, calculated by CASTp webserver, of the Ketanserin-bound 5-HT<sub>2A</sub>R trajectory at frames corresponding to **Fig6C-G**.